REMARKS

I. Claim Changes

Claim changes have been made in method claims 32 to 44 and bioadhesive tablet claims 45 to 53 to eliminate some minor formal wording errors, such as numerical errors and spelling errors. However the subject matter and scope of the previously pending claims has not been changed.

An error in the ratio of testosterone to said one or more testosterone ester in dependent claims 35 and 48 has been corrected. This change has basis in the fifth full paragraph on page 5 of the applicants' specification. Misspellings in claims 43 and 44 and an antecedent basis error in claim 42 have been corrected.

The features and limitations of claims 32, 34 and 35 have been included in method claim 36 so that claim 36 is now an independent method-of-making-a-bioadhesive-tablet claim. This amended claim 36 claims the preferred embodiment in which the method produces a bioadhesive tablet including both testosterone and at least one testosterone ester. Also the features and limitations of claims 45, 47 and 48 have been included in bioadhesive tablet claim 49 so that claim 49 is now an independent bioadhesive tablet claim. This amended bioadhesive tablet claim 49 claims the preferred embodiment in which the bioadhesive tablet includes both testosterone and at least one testosterone ester. Also "and/or" in claims 36 and 49 has been changed to "and" and "optionally" has been inserted in these claims to correct inconsistencies.

Dependent method claims 38, 41, 42, 43 and 44 have been amended so

that they now depend on newly amended independent method claim 36 as well as claim 32. Dependent bioadhesive claims 51 to 53 have been amended so that they now depend on newly amended independent bioadhesive tablet claim 49 as well as claim 45.

New method claims 54 to 59 have been added as well as new bioadhesive tablet claims 60 to 65. These claims limit claims 32 and 45 to embodiments of the method and bioadhesive tablet, which necessarily a method of producing a bioadhesive tablet or a bioadhesive tablet including at least one testosterone ester.

Also a Declaration containing additional comparative evidence accompanies this amendment. It is provided to help overcome the rejection of the method and table claims as obvious over Voorspoels, et al, and the KR reference. The Declaration contains comparative experimental results showing that a tablet containing testosterone ester in an amorphous form is unexpectedly better at dispensing the testosterone ester during buccal administration than a corresponding tablet containing the testosterone ester in crystalline form, which is made by mechanical mixing according to the prior art. This shows that much greater bioavailability is expected for the testosterone ester when tablets made by applicants' claimed method are administered.

The Declaration especially contains evidence for the allowability of new claims 54 to 65 and especially amended independent claims 36 and 49, i.e. claims for a bioadhesive tablet necessarily containing at least one testosterone ester or claims for making that bioadhesive tablet.

II. Obviousness Rejections based on Voorspoels and the KR Abstract

Claims 32 to 38 and 45 to 51 were rejected as obvious under 35 U.S.C. 103 (a) over Voorspoels, et al, in view of KR 9606729.

A. Claims limited to Bioadhesive Tablets containing at least one Testosterone Ester and Methods of Making Them

New dependent claims 54 to 65 are limited to methods of making bioadhesive tablets and bioadhesive tablets that necessarily contain at least one testosterone ester – with or without testosterone present. That is the only difference between the coverage provided by claim 54 and claim 32. Similarly method claim 36 and bioadhesive tablet claim 49 have now been amended so that they are independent and claim embodiments limited to bioadhesive tablets containing both testosterone and at least one testosterone ester.

In this section it will be shown below that a *prima facie* case of obviousness cannot be established for new claims 54 to 65 using Voorspoels, et al; and KR 9606729. In the same way it will be shown that the rejection of claims 36 and 49 and the claim subject matter now dependent on these claims as obvious under 35 U.S.C. 103 (a) over Voorspoels, et al; and/or the above KR reference should be withdrawn.

First, one skilled in the art would not be motivated by the results in Voospoels, et al, to replace any portion of the testosterone in a bioadhesive tablet for buccal administration containing testosterone by a corresponding amount of one or more testosterone esters.

Voorspoels, et al, contains teaching against the invention as claimed in new claims 54 to 65. Voorspoels, et al, teaches buccal administration of a bioadhesive tablet, which contains either testosterone or a testosterone ester. They concluded from their experimental results that the bioavailability of testosterone provided by this type of bioadhesive system is significantly greater than that of the tested testosterone esters, which include testosterone propionate and testosterone decanoate. Thus one skilled in the art would not replace a portion of the testosterone in this type of bioadhesive tablet or make a bioadhesive tablet containing a testosterone ester instead of testosterone, because according to the results of Voorspoels, et al, an equivalent amount of testosterone would be better absorbed and more available. Thus testosterone would be more effective than a similar amount of the testosterone ester in the bioadhesive tablet, according to Voorspoels, et al.

It is well established that a reference that teaches away or leads one skilled in the art away from the claimed invention should not be used alone or in combination with other references to reject a claimed invention under 35 U.S.C. 103 (a). See for example M.P.E.P.2145 X. D. 3. Also the Federal Circuit Court of Appeals has said:

> "In determining whether such a suggestion [of obviousness] can fairly be gleaned from the prior art, ..It is indeed pertinent that these references teach against the present invention. Evidence that supports, rather than negates, patentability must be fairly considered." ***In re Dow Chemical Co.,*** 837 F.2nd 469,473, 5 U.S.P.Q.2d 1529, 1532 (Fed.Cir. 1988)

One skilled in the art, who accepted the results of Voorspoels, et al, would

not replace any part of the testosterone in a bioadhesive tablet for buccal administration of testosterone with testosterone ester because those results teach that such a tablet would be less effective when administered to perform its intended purpose.

Furthermore one skilled in the art, who accepted the results of Voorspoels, et al, would be unlikely to try to mix testosterone esters with testosterone in a bioadhesive system for buccal administration to extend the time over which testosterone is delivered. The results of the reference on page 1230 and in fig. 2 and figs. 3a to 3d show that the bioavailability of testosterone esters administered by means of the bioadhesive tablet is only very small, below 3 % (page 1230, line 27, left hand column). The measured bioavailability of testosterone esters obtained by means of the bioadhesive tablet prepared by Voospoels, et al, (figs. 3a to 3d) is comparable to the bioavailability obtained by oral administration of a bioadhesive tablet containing an equivalent amount of testosterone itself (fig. 2 circles) Thus according to this reference modification of the delivery profile of testosterone by including testosterone esters would not be practical because the amounts of testosterone esters in relation to testosterone would necessarily be excessive, which impairs the adhesion of the bioadhesive tablet.

The "Introduction" of this reference teaches that at the time of its publication the oral administration route (which does not include the use of a bioadhesive tablet) for testosterone had been abandoned because bioavailability by this method was too low. Furthermore the "Introduction" states that at the time

it was not possible to simulate the circadian rhythm of testosterone plasma levels in healthy men by any method of administration (first two lines of right hand column of p. 1228). The results for bioavailability in figs. 2 and 3a to 3d of Voorspoels, et al, would suggest to one skilled in the art that the solution to the problem of simulating the circadian rhythm of testostoterone is clearly **not** to prepare bioadhesive tablets for buccal administration containing a mixture of at least one testosterone ester with or without testosterone itself.

Thus one skilled in the art would not be motivated to prepare bioadhesive tablets that necessarily contain one or more testosterone esters for buccal administration (as claimed in new dependent claims 54 to 65) to augment the testosterone plasma levels or to simulate the circadian rhythm of testosterone plasma levels.

In contrast, applicants have found that the bioavailability of testosterone can be significantly increased and extended when a mixture of testosterone and at least one testosterone ester is administered buccally by means of a bioadhesive tablet, provided that the bioadhesive tablet is prepared by the method claimed in claim 32. This preparation method comprises a spray-drying technique to prepare an intermediate amorphous active ingredient mix containing the testosterone and/or testosterone ester in its amorphous or non-crystalline form. This differs from the method of making the bioadhesive tablet according to Voorspoels, et al. The method of making the bioadhesive tablets used by Voorspoels is described in the right hand column of p. 1228. Testosterone and testosterone esters were obtained commercially and were crystalline, not

amorphous. The active ingredients were mechanically mixed with CARBOPOL®, sodium stearyl fumarate and waxy maize (filler). The mixture was then compressed to form a tablet.

Because the tablets of Voorspoels, et al, are the result of a mechanical mixing of the crystalline active ingredients with other ingredients, the tablet essentially contains the active ingredients in their crystalline form embedded in the filler, binder and other ingredients. In contrast, the spray-drying method of the applicants produces a composition in which the active ingredients are present in their amorphous (non-crystalline) form, which is more soluble in water or saliva, than the corresponding crystalline form. This latter fact is supported by the solubility results in the accompany Declaration.

Because of the greater solubility during the time available for buccal administration, the bioavailability of the testosterone esters is greater (see page 4, last four lines of the paragraph beginning "Surprisingly" of applicants' speficiation) when the bioadhesive tablet prepared by the method of the invention is employed. In contrast to the statements in the "Introduction" of Voorspoels, et al, it is now possible to simulate the circadian rhythm of testosterone plasma levels in healthy men by buccal administration of a tablet containing mixtures of testosterone and testosterone esters, especially testosterone undeconate (see figs. 1 to 3 of applicants' specification). This is possible because the bioavailability of the esters in the tablets prepared by the method of claim 32 is much greater than that of the method used in Voospoels, et al, which is based on mechanical mixing of ingredients including testosterone or a testosterone ester in

its commercially available crystalline form.

Fig. 3 of applicants' specification show the variation of the testosterone concentrations in the blood of a female dog with time over a time period of about half a day after buccal administration of a mixture of testosterone and testosterone undecanoate. The buccal administration starts with the application of a bioadhesive tablet prepared in example 3 of applicants' specification, as described in the last paragraph on page 5 of applicants' specification.

After the application of the bioadhesive tablet of example 3 the peak serum testosterone concentration of about 260 ng/ml was reached within one half hour (which is also true of a tablet that one contains testosterone alone – see fig. 1). Then the testosterone concentration decreases rapidly within the first two hours to values of about 100 ng/ml. In the case of the table of example 3 containing both the undecanoate ester as well as testosterone itself a second peak at about 120 ng/ml is reached after about 3 hours (also similar to fig. 1). However then the testosterone concentrations decreased more slowly than when the bioadhesive tablet containing testosterone alone is administered. After 8 hours the testosterone concentration values of nearly 50 ng/ml attained with the bioadhesive tablet containing both testosterone and testosterone undecanoate are still twice as high as those attained with the bioadhesive table containing testosterone alone. Thus in contrast to the statement in the introduction of Voorspoels, et al, it is possible to maintain physiological testosterone blood level patterns or simulate circadian rhythms for about 12 hours by buccal administration of a mixture of testosterone and testosterone ester, when the

bioadhesive tablet employed is prepared according to the method of new dependent claims 54 to 59.

KR 9606729 discloses that tablets for oral adhesive administration can be prepared by mixing active ingredients with polymer solutions, including hydroxypropyl cellulose solutions, spray-drying the solutions to make a micropellet and then tableting the micropellet.

However neither the KR reference nor Voorspoels, et al, discloses or suggests that the spray-drying method will produce a tablet containing one or more testosterone ester with or without testosterone itself for buccal administration to augment testosterone plasma levels that provides significantly higher bioavailability and concentrations of the testosterone in body fluids, such as blood.

There are many different possible alternative administration methods for testosterone and its esters, as explained in the "Introduction" of Voorspoels, et al. These methods include intravenous and intramuscular routes. There are many different parameters that can be varied in all of these methods, such as choice of auxiliary ingredients, concentrations of ingredients and particular chemical compounds used to delivery testosterone. Attempts also might be made to try to find special chemical ingredients that would assist in absorption of the testosterone esters from tablets made by the simpler mechanical mixing methods of Voorspoels, et al.

There is no reasonable hint or suggestion in either reference that would lead one skilled in the art to change the method of preparation of the bioadhesive

table from the simple mechanical mixing method of Voorspoels, et al, to the more complicated spray-drying method of the KR reference. Furthermore the two references provide not the slightest hint or suggestion regarding how to improve the bioavailability of testosterone provided by administration of testosterone esters, which is shown to be very poor by the experimental results of Voorspoels, et al.

In any case neither the KR reference nor Voorspoels, et al, consider the effect of different methods of preparing bioadhesive tablets for buccal administration on the bioavailability of active ingredients included in the tablets. Particularly the KR reference merely teaches an alternative way to prepare a tablet, but does **not** disclose or suggest that the spray-drying method of making a bioadhesive tablet containing a testosterone ester will increase the bioavailability of the testosterone when a bioadhesive tablet containing a mixture of a testosterone ester and testosterone is administered.

Merely because references can be combined to produce a claimed method is not enough to provide a basis for a rejection under 35 U.S.C. 103 (a). The references must provide a hint or suggestion of the modifications necessary to arrive at the claimed invention. In other words, the references must provide a suggestion of the desirability of making the particular modifications necessary to obtain the claimed invention.

In the present situation the fact that active ingredient can be released continuously, as mentioned in the Office Action, is not enough to suggest switching to the spray-drying technique, because figs. 3a to 3d of Voorspoels, et

al, show that the esters are released continuously, although in only very small amounts.

Also the fact that the tablet made by spray-drying also has sufficient adhesion ("good" adhesion) for buccal administration is also not enough to suggest switching to the more laborious spray-drying technique because there is no suggestion in Voorspoels, et al, that the bioadhesive tablets that they made by the simpler mechanical mixing method did not have adequate adhesion. In fact, Voorspoels, et al, measured the adhesion force of various bioadhesive tablets on Porcine gingival (p. 1229 of Voorspoels) and found that the adhesive force decreases as the amount of ester in the tablet increases (see Fig. 1). However Voorspoels, et al, successfully administered amounts of testosterone decanoate equivalent to 60 mg of testosterone with a bioadhesive tablet prepared by the method described on page 1229 of this reference. The resulting blood plasma levels of testosterone from this latter administration were successfully measured. Thus the bioadhesion of the tablets made by the method of Voorspoels, et al, which were never described as inadequate in the reference, were certainly adequate for delivery of the higher alkyl esters of testosterone. Thus one skilled in the art would not be motivated to seek another method of preparation of the bioadhesive tablet different from that described in Voorspoels, et al, or to replace that method with the method of the KR reference for that reason. There is no hint or suggestion to change to the more laborious spray-drying method of the KR reference in either reference, especially since there is not disclosure related to testosterone esters in the KR reference.

It is well established by many federal judicial decisions that to reject a claimed invention under 35 U.S.C. 103 there must be some hint or suggestion in the prior art of the modifications of the disclosure in a prior art reference or references used to reject the claimed invention, which are necessary to arrive at the claimed invention. For example, the Court of Appeals for the Federal Circuit has said:

> "Rather, to establish obviousness based on a combination of elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant...Even when obviousness is based on a single reference there must be a showing of a suggestion of motivation to modify the teachings of that reference.." *In re Kotzab*, 55 U.S.P.Q. 2nd 1313 (Fed. Cir. 2000). See also M.P.E.P. 2141.

Although the KR reference does teach a spray-drying method for making bioadhesive tablets for buccal administration, which include active ingredients in general, there is no hint or suggestion in the KR reference that switching from the simpler mechanical method of making the tablets for buccal administration disclosed in Voorspoels, et al, to a spray-drying method like that disclosed in the KR reference would result in greater bioavailability and higher testosterone plasma concentrations when the active ingredients include at least one testosterone ester.

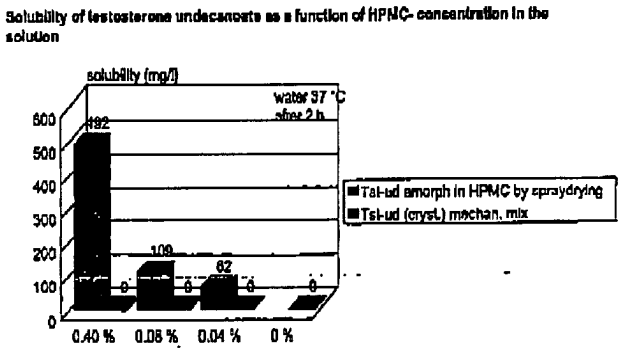
Thus it is respectfully submitted that a combination of Voorspoels, et al, with the KR reference does not establish a case of *prima facie* obviousness of applicants' claims, at least of new dependent claims 54 to 65.

Also comparative experimental results are available which should overcome any alleged case of *prima facie* obviousness. The experimental results shown in applicants' fig. 3 regarding the testosterone concentrations produced in the blood by buccal administration of a mixture of testosterone and testosterone undecanoate contradict the statement in the "Introduction" of Voorspoels, et al, that there is no method of administration to testosterone or testosterone esters that simulates the circadian rhythm of testosterone plasma levels, i.e. maintains and extends the delivery of testosterone over a 12 hour period in a therapeutic method of treating various conditions in men.

Furthermore additional experimental solubility results have shown that the solubility (2 hours after administration) of testosterone esters in a fluid similar to the saliva present in the oral cavity is considerably greater when the testosterone esters are originally present in a tablet prepared according to the method of claim 54 or 32 than when the tablet is prepared by the method disclosed in Voorspoels, et al. Presumably the difference is due to the fact that the testosterone esters of Voorspoels, et al, were obtained commercially and were in the crystalline state, while the spray-drying procedure of the applicants produces a tablet which contains testosterone esters in the amorphous state (see page 4, last paragraph of applicants' specification).

A graphical illustration (bar graph) showing the results appears in the accompanying Declaration and below. It compares solubilities (two hours after administration) of amorphous testosterone undecanoate from a bioadhesive tablet made by the method of new dependent claim 54 (with HPMC as organic

polymer) and a bioadhesive tablet of the prior art (Voorspoels, et al) made by mechanical mixing of crystalline testosterone undecanoate and HPMC. The solubilities for the invention and the prior art are shown as a function of HPMC concentrations in solution. The bars with zeros are for the prior art and they show that even when the solubility of HPMC is close to 1 % in the solution, no testerone undecanoate dissolves from the tablet. In contrast, in the case of the tablet made by spray-drying according to the invention a solubility of 492 mg/l of testosterone undecanoate results in water at 37°C (body temperature) after two hours.



In the case of the tablet according to the invention the solubility of testosterone undecanoate increases with increasing amounts of HPMC in the solution, while in the case of the tablet of the prior art (made by the method of Voorspoels, et al), the solubility does not increase with increasing concentration of HPMC in the solution and is practically zero.

Thus during buccal administration a high super-saturation solubility of testosterone undecanoate is produced at the moist resorption surfaces, namely

the oral mucosa, when the tablet according to the present invention (claim 54) is employed. The higher the concentration of the adjuvant substance (HPMC), the higher the super-saturation concentration.

This means that despite the comparatively small solubility of testosterone undecanoate in pure water a comparatively large amount of testosterone undecanoate from the tablet made by embedding in HPMC dissolves in saliva in the mouth. Thus the concentration gradient of testosterone undecanoate produced by the tablet according to the invention at the resorption surfaces in buccal administration is comparatively much larger than that produced by the tablet made by the method of Voospoels, et al.

These comparative solubility results are included in the accompanying Declaration together with the graphical illustration showing the solubilities. The copy of the Declaration that accompanies this amendment is unsigned, but a signed copy will be obtained and filed as soon as possible.

For the foregoing reasons it is respectfully submitted that new claims 54 to 65 should not be rejected under 35 U.S.C. 103 (a) over Voorspoels, et al, in view of KR 9606729 (KR).

Also withdrawal of the rejection of amended independent claims 36 and 49 and the claim subject matter dependent on them under 35 U.S.C. 103 (a) over Voorspoels, et al, in view of KR 9606729 (KR), is respectfully requested.

B. Claims 32 and 45

Claims 32 and 45 have not been changed.

The sole difference between method claim 54 and claim 32 is that the

active ingredient in the case of claim 32 could consist of testosterone only in the case of some embodiments. The same is true of the table of claim 45: the active ingredient could consist of only testosterone without any of its esters.

Voospoels, et al, leads one skilled in the prior art away from the invention claimed in method-of-making-a-bioadhesive-tablet claim 32. The method of making the bioadhesive tablets used by Voorspoels, et al, is described in the right hand column of p. 1228 of that article. Testosterone and testosterone esters were obtained commercially and were crystalline. The active ingredients were mechanically mixed with CARBOPOL®, sodium stearyl fumarate and waxy maize (filler). The mixture was then compressed to form a tablet.

Because the tablets of Voorspoels, et al, are the result of a mechanical mixing of crystalline active ingredients with auxiliary ingredients, the tablet essentially contains the active ingredients in their crystalline form embedded in the filler, binder and other ingredients. This is the opposite from the claimed invention in claim 32. The method of claim 32 produces a tablet in which the active ingredient, testosterone, is embedded in amorphous form in the organic binder and other ingredients.

Claim 32 itself clearly states that "an amorphous active ingredient premix" is formed first. This is the opposite from the method of making bioadhesive tablets described in Voorspoels, et al.

As noted above a reference that teaches the opposite from a claimed invention cannot be combined with other references to reject the claimed invention under 35 U.S.C. 103 (a). Again see M.P.E.P. 2145 X.

Furthermore the arguments above regarding the lack of motivation in the cited references, Voorspoels, et al, and the KR reference, for one skilled in the art to change the method of making the bioadhesive tablet from a simple grind and mix method to the more laborious spray-drying method are applicable to the case of both method claim 32 and bioadhesive tablet claim 45.

There must be some hint or suggestion in the art regarding the desirability to combine the references in the suggested manner in order for a valid rejection under 35 U.S.C. 103 (a). Here it is respectfully submitted that the reasons for motivating combination of the references described on page 3 of the Office Action would be insufficient for one of ordinary skill in the art. For one of ordinary skill in the art there would be no motivation to change the method of making the tablet of Voorspoels, et al, from the simpler mechanical mixing method to the more laborious spray-drying method because the tablets of Voorspoels, et al, have sufficiently good adhesion and also continuously release the active agent.

The test for combinability of features from one reference with those of another reference is not that the features can be combined but that the art suggests that the combination should be made. There is no such suggestion in either of these cited prior art references.

In view of the foregoing reasons withdrawal of the rejection of amended claims 32 to 38 and 45 to 51 as obvious under 35 U.S.C. 103 (a) over Voorspoels, et al, in view of KR 9606729, is respectfully requested.

III. Obviousness Rejection of Claims 39 to 44 and 52 and 53

Claims 39 to 44 and 52 and 53 were rejected as obvious under 35 U.S.C. 103 (a) over Voorspoels, et al, in view of KR 9606729 (KR), and further in view of Timpe, et al.

These claims have not been changed, and they claim the embodiments of the method and tablet, in which the tablet is a bi-layer tablet with an adhesive layer and an active-ingredient containing layer. Timpe, et al, does disclose a bi-layer tablet structure for buccal administration comprising an adhesive layer and an active-ingredient containing layer.

Timpe, et al, do **not** suggest or disclose the key distinguishing feature of the method of manufacturing according to claim 32, namely the formation of an intermediate premix, i.e. the amorphous active ingredient premix, by spray-drying a solution of the active ingredient and polymeric binder in an organic solvent. Examples 1 to 3 in column 6 of Timpe, et al, clearly state that the ingredients of the tablets are mixed mechanically and molded into tablets in the known way. See also column 4, lines 13 to 22; column 4, lines 50 to 60, which support this conclusion.

Also Timpe, et al, clearly do not suggest that the spray-drying feature for making the intermediate active ingredient premix provides better bioavailability of testosterone esters during buccal administration. Thus applicants' method claims are not *prima facie* obvious from the combination of Voorspoels, et al, the KR

reference and Timpe, et al.

For the foregoing reasons withdrawal of the rejection of claims 39 to 44, 52 and 53 under 35 U.S.C. 103 (a) as obvious over Voorspoels, et al, and KR 9606729, and further in view of Timpe, et al, is respectfully requested.

Should the Examiner require or consider it advisable that the specification, claims and/or drawing be further amended or corrected in formal respects to put this case in condition for final allowance, then it is requested that such amendments or corrections be carried out by Examiner's Amendment and the case passed to issue. Alternatively, should the Examiner feel that a personal discussion might be helpful in advancing the case to allowance, he or she is invited to telephone the undersigned at 1-631-549 4700.

In view of the foregoing, favorable allowance is respectfully solicited.

Respectfully submitted,

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